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Original Research Paper

Influence of solvent mixtures on HPMCAS-celecoxib microparticles prepared by electrospraying[☆]

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ABSTRACT

Hypromellose acetate succinate (HPMCAS) microparticles containing the poorly-water soluble drug celecoxib (CEL) were prepared by electrospraying intended for oral drug delivery. Various solvent mixtures with different solubility for CEL and HPMCAS were used to induce changes in the polymer structural conformation of the microparticles. The performance of the prepared microparticles was evaluated by studying the solid state from, particle size and morphology, radial drug distribution and drug release. CEL was amorphous in all electrosprayed HPMCAS microparticles. The particle size and morphology was dependent on the solubility of HPMCAS in the solvent mixture used with poorer solvents resulting in smaller microparticles with rougher appearance. The CEL distribution on the particles surface was relatively homogeneous and similar for all microparticles. Drug release from the microparticles was observed at a higher rate depending on the solubility of HPMCAS in the solvent used for electrospraying, and in all cases an at least 4-fold higher rate was observed compared with the crystalline drug. Drug precipitation from the supersaturated solution was inhibited by HPMCAS for all microparticles based on its parachute effect while crystalline CEL did not reach supersaturation. This study demonstrated that electrospraying can be used to produce microparticles with tailored properties for pharmaceutical application by adjusting solvent selection.

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Abbreviations: ACE, acetone; BCS, biopharmaceutics classification system; b.p., boiling point; EtOH, ethanol; H₂O, water; HPMCAS, hypromellose acetate succinate; PBS, phosphate-buffered saline; SD, standard deviation; SEM, scanning electron microscopy; SLS, sodium lauryl sulphate; XRPD, X-ray powder diffraction.

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1. Introduction

A large fraction of drug compounds under development are limited by their poor water solubility [1]. Their poor solubility in aqueous media (including body fluids) often results in a low and variable oral bioavailability and hence unsatisfactory therapeutic performance of the drugs [2–4]. There are many approaches to balance the poor solubility of drugs, where drug-loaded polymer microparticles continue to be of interest. A solid dispersion system is defined as a mixture of at least two components, the drug substance and a matrix excipient [5], where the drug is highly dispersed in the matrix, typically in a molecular form increasing the dissolution rate and bioavailability of the drug from its formulation [6]. Solid dispersions are particularly favorable for drugs with low gastrointestinal solubility but high permeability [7,8]. These are classified as BCS class II drugs and typically show a correlation between *in vitro* solubility and *in vivo* bioavailability [9].

The matrix material plays a significant role in solid dispersions and influences characteristics such as particle size, drug devitrification rate, wettability, drug dispersability, and dissolution behavior [6,10,11]. Hypromellose acetate succinate (HPMCAS) is a cellulose derived polymer, which is commonly utilized as an enteric coating agent due to its pH-dependent solubility in aqueous environments. Moreover, HPMCAS has demonstrated to be an effective precipitation inhibitor preventing salt recrystallization and prolonging the supersaturation of drugs for several hours after dissolution. The pronounced effect of HPMCAS is explained by the formation of nanosized amorphous drug-polymer aggregates resulting from its particle ionized state and from hydrophobic interactions [12,13]. Much indicates that such precipitation inhibition may provide considerable improvements in the *in vivo* performance of such formulations [14].

Currently, two major processes are used in the manufacturing of solid dispersion systems, melting methods and solvent evaporation methods [8,15]. Many solid dispersion dosage forms consist of microparticles due to the preparation methods employed. Their microstructure can have an influence on the release kinetics, efficacy and the physical stability of the drug and should thus be optimized to improve the general performance of the formulations [16,17].

In this study, electrospraying was used as a method for producing microparticulate solid dispersions. Electrospraying is a liquid atomization technique utilizing a strong electric potential to disrupt the liquid feed into small droplets resulting in near-monodisperse microparticles [18,19]. Notably, electrospraying has found potential use in the biomedical field, where tailored properties of utilized drug delivery vehicles or diagnostic probes are of significant relevance for therapy and diagnosis [20,21]. Adjusting the different process parameters using electrospraying allows for tailored particle engineering. Yet, the process is complex due to the interplay between different interdependent parameters, which influence the characteristics of the resulting microparticles [22,23]. For instance the selection of solvent influences both the spray ability of the liquid feed and the resulting droplet dimensions, based on characteristics such as surface tension and electric conductivity, but also influences the particle characteristics, based on

the solubility of materials dissolved or suspended in the solvent [24–26].

In the current study, we investigated different solvent mixtures for preparing a solid dispersion system of HPMCAS together with a model drug, CEL, by electrospraying. CEL is a crystalline, non-steroidal anti-inflammatory drug, and both its aqueous solubility ($\sim 5 \mu\text{g/ml}$) and solubility-limited bioavailability are low [27]. The obtained microparticles were thoroughly examined by means of X-ray powder diffraction (XRPD) and scanning electron microscopy (SEM) and the surface drug distribution of the microparticles was determined using X-ray photoelectron spectroscopy (XPS). Further, the *in vitro* drug release and precipitation inhibition was also investigated for solid dispersions prepared using distinct solvents and solvent mixtures.

2. Materials and methods

2.1. Materials

The HPMCAS (AQOAT) LF grade was acquired from Shin Etsu (Tokyo, Japan). CEL powder was purchased from Dr. Reddy (Hyderabad, India). Acetone (ACE, 99.9% HPLC grade), ethanol (EtOH, 99.9% HPLC grade) and acetonitrile (99.9% HPLC grade) were purchased from Sigma Aldrich (Poole, UK). Phosphate-buffered saline (PBS, 0.01 M, pH 6.8) was prepared from sodium phosphate monobasic and sodium hydroxide acquired from Sigma Aldrich. Sodium lauryl sulphate (SLS) was acquired from Fagron (Waregem, Belgium) and ultrapure water (SG Water Purification System, Barsbüttel, Germany) was used for all experiments. All other chemicals and solvents were of analytical grade and were used without further purification.

2.2. Solubility test

The solubility of HPMCAS and CEL, in ACE, EtOH, water and mixtures of these solvents was evaluated at room temperature ($\sim 25^\circ\text{C}$) by placing 0.5 g of the polymer or drug into 10 ml of solvent mixture and mixing using a magnetic stirrer. The degree of dissolution was further assessed visually after 1 and 24 h, and if failing to form a complete solution, the mixture was diluted with more solvent (10 ml) and if successfully dissolved more solute was added [15,28]. The solubility of solutes in the different solvent mixtures was rated according to a common classification as freely soluble (100–1000 mg/ml), soluble (33–100 mg/ml) and practically insoluble ($< 0.1 \text{ mg/ml}$) [29,30].

2.3. Preparation of microparticles

Solutions of HPMCAS and CEL were prepared at a solute concentration of 5% (w/v) and a drug loading of 20% (w/w) in different solvents including ACE, ACE–EtOH (85:15, v/v), ACE–H₂O (85:15, v/v), EtOH–H₂O (85:15, v/v). CEL-loaded HPMCAS microparticles were prepared using a customized single nozzle electrospraying setup with the same configurations as previously described [31]. Briefly, the electrospraying setup essentially consisted of a high voltage electrical power source (Glassman Europe Ltd., Tadley, UK), a precision syringe pump



Fig. 1 – Jet image captured during electro spraying in cone-jet mode.

(Elite, Harvard Apparatus, Edenbridge, UK), a spraying and collection platform and a custom-built stainless-steel nozzle with an outer and inner diameters of 2.34 and 1.77 mm, respectively. The feed solutions were electro sprayed at a voltage of 7–8 kV in the stable cone-jet mode by a feed rate of 30 μ l/min. Microparticles were collected at a distance of 7 cm from the nozzle tip. Only microparticles prepared by a stable cone-jet (Fig. 1) were collected. All samples were prepared in triplicates under room temperature, and stored in a desiccator at room temperature.

2.4. XRPD

The X-ray powder diffraction spectra were detected by a PW3040/60 X' Pert Pro MPD (PANalytical, Philips, Netherlands) equipped with a copper anode for radiation with $\lambda = 1.542 \text{ \AA}$, 45 kV and 40 mA. The samples were placed on aluminum sample holders and measured from 5 to 35° 2θ at a step of 0.053° and 0.025° per second.

2.5. SEM

The electro sprayed microparticles were collected on glass slides, mounted on stubs with double-sided carbon tape and sputter-coated with a $\sim 5 \text{ nm}$ layer of gold using a Leica EM ACE200 (Wetzlar, Germany). Images were acquired using an FEI/Philips XL30 FEG (Hillsboro, USA) at an acceleration voltage of 3 kV using the secondary electron detector. The size of microparticles was obtained by averaging the diameter of 200 microparticles using the software ImageJ (National Institute of Health, Maryland, US).

2.6. XPS

The surface chemistry of the microparticles was analyzed using XPS (Thermo Scientific, Roskilde, Denmark) equipped with a monochromated AlK α X-ray source. Survey scans of

0–1350 eV binding energy were performed using a pass energy of 200 eV and a step size of 1.0 eV and at a 90° take-off angle. The surface drug content of the microparticles was determined by correlating the ratio of the detected fluorine in the samples to the fluorine in CEL alone thereby determining the concentration of CEL (in wt %) on the surface of the microparticles. The atomic concentration (in %) of elements C, O, F, N and S in CEL is 65.4%, 7.7%, 11.5%, 11.5% and 3.9%, respectively. To minimize error, ratios of N/F, S/F and F/C were used to calculate the concentration of CEL at the microparticle surface.

2.7. Drug loading efficiency and HPLC

The microparticles were dissolved in 1 ml acetonitrile and diluted in 1:10 (v/v) water for determining the concentration of CEL in the microparticles. The CEL concentration was measured by reverse-phase HPLC (Dionex, Germering, Germany) coupled with a P680 pump, ASI 100 sample injector, UVD340U detector (Dionex, Germering, Germany), and a C18 Kromasil 126 column (Bohus, Sweden). A mobile phase of acetonitrile-H₂O (60:40, v/v) was used at a constant flow rate of 0.5 ml/min and samples were injected with a 10 μ l injection volume and detected at a wavelength of 230 nm. The drug loading efficiency was calculated as:

$$\text{Drug loading (\%)} = (\text{Drug mass} / \text{Particle mass}) \times 100$$

2.8. Drug release study

Drug release from the electro sprayed solid dispersions was studied using a USP paddle Apparatus II. Approximately 25 mg microparticles were accurately weighted and placed in glass vessels fixed in a Sotax AT7 dissolution station (Sotax, Allschwil, Switzerland). Then, 900 ml release medium of phosphate buffered solution (pH 6.8) with or without 1.5% (w/v) SLS was added, and constantly stirred by a paddle at a rotation rate of 50 rpm at 37 °C. SLS was added to obtain sink condition for CEL. At each sample point 5 ml release medium was sampled through a 2.7 μ m glass microfiber filters (Whatman Ltd., Oxon, England) by a Biolab/Gilson GX-271 auto sampler (Biolab, Gloucestershire, UK). The vessels were added 5 ml fresh release medium to maintain their volume. Release samples were analyzed by HPLC as outlined above. The release from microparticles was compared with dissolution rate of crystalline CEL powder and the release from the physical mixture of HPMCAS and CEL.

2.9. Statistics

All experiments were performed in triplicate ($n = 3$) except for particle size measurements where 200 microparticles were measured, and the results were indicated by mean value \pm SD.

3. Results and discussion

Electro spraying is a one-step processing technique for preparation of microparticles, which does not involve elevated temperatures as with spray-drying [32,33]. In order to prepare

Table 1 – Solubility of HPMCAS and CEL, in pure solvents and solvent mixtures. Solubility is given as, freely soluble (++), soluble (+) and practically insoluble (–).

Solvents	HPMCAS	CEL
ACE	++	++
EtOH	–	+
H ₂ O	–	–
ACE–EtOH (85:15)	++	++
ACE–H ₂ O (85:15)	+	+
EtOH–H ₂ O (85:15)	+	+

a solid dispersion system with electrospraying using a hydrophilic polymeric and poorly water-soluble drug solvent selection should be considered along with the solubility of the drug and polymer in the solvent [23,34]. Further, not all solvents and compounds are compatible with electrospraying, due to constraints with regards to surface tension, viscosity and electrical conductivity [35]. In this study HPMCAS and CEL have different solubilities in the distinct solvents, and solvent mixtures were thus investigated to assess their influence on the characteristics of resulting microparticles and their performance. ACE and three solvent mixtures, ACE–EtOH, ACE–H₂O and EtOH–H₂O, were examined, and were demonstrated to have an influence on the particle size, particle morphology, drug distribution and release behavior, which are presented and discussed below.

3.1. Solubility of HPMCAS and CEL

The solubility of HPMCAS and CEL in ACE, EtOH, water and their mixtures was studied. It was observed that ACE is a good solvent for both HPMCAS and CEL (Table 1) dissolving up to 200 mg/ml HPMCAS and 600 mg/ml CEL. Adding water or EtOH to the ACE solution containing HPMCAS and CEL decreased their solubilities. The same applied for CEL when water was added to the EtOH solution, whereas in the case of HPMCAS its solubility increased. CEL is practically insoluble in water whereas HPMCAS is sparingly soluble in water and EtOH individually. For a 50 mg/ml HPMCAS solution with CEL (20%, w/w) a stable solution was obtained in ACE–H₂O mixtures up to a H₂O content of 50:50 (v/v), whereas for ACE–EtOH mixtures a stable solution was obtained at even higher EtOH contents. In

Table 2 – Characteristics of electrosprayed CEL-loaded HPMCAS microparticles.

Solvent	Size (μm)	Drug entrapment (%)
ACE	3.4 ± 0.7	96 ± 4
ACE–EtOH (85:15)	3.5 ± 0.7	98 ± 3
ACE–H ₂ O (85:15)	3.0 ± 0.6	101 ± 3
EtOH–H ₂ O (85:15)	2.7 ± 0.5	97 ± 4

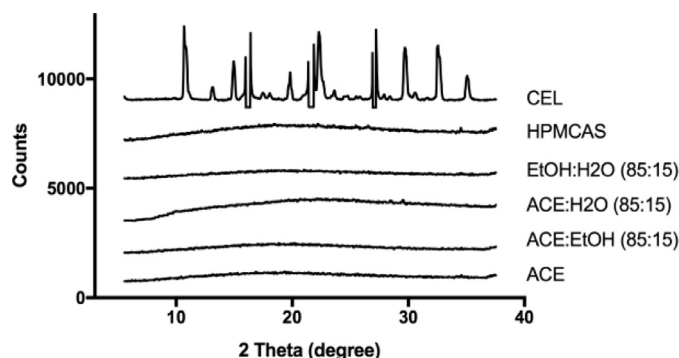
EtOH–H₂O mixtures CEL was soluble up to a H₂O content of 75:25 (v/v) indicating that in some mixtures the solubility is limited by HPMCAS whereas in others it is limited by CEL. Finally, a ratio of 85:15 (v/v) was selected for all three solvent mixtures (ACE–H₂O, ACE–EtOH, EtOH–H₂O) as electrospraying feed solutions, for which both HPMCAS and CEL could be completely dissolved.

Due to the solvent ratio-dependent solubility of HPMCAS and CEL it was expected to observe differences in particle formation for microparticles prepared using different solvent mixtures. Differences in the evaporation rate of the solvents used, is likely to result in earlier or later precipitation of HPMCAS and CEL. For instance, since ACE (b.p. 56 °C) evaporates quicker than EtOH (b.p. 78 °C) and EtOH evaporates quicker than H₂O, the increasing EtOH and H₂O content in the evaporating droplet could result in selective precipitation of HPMCAS or CEL.

3.2. Characterization of microparticles

XRPD patterns for CEL, HPMCAS and electrosprayed samples are presented in Fig. 2 and show that while unprocessed CEL exhibited crystalline features, a halo pattern was observed for all electrosprayed samples indicating that CEL exists in the amorphous form in the microparticles.

The size of electrosprayed CEL-loaded HPMCAS microparticles from pure ACE and three co-solvent systems are shown in Table 2, indicating that all the microparticles were of similar size, ranging from 2 to 4 μm in diameter. Microparticles prepared with ACE and ACE–EtOH were larger than those prepared with ACE–H₂O, which were larger than those prepared with EtOH–H₂O. This trend can be explained from the solubility of HPMCAS in the different solvent mixtures, where the better solvent mixtures resulted in larger microparticles com-

**Fig. 2 – XRPD patterns of CEL, HPMCAS and electrosprayed CEL-loaded HPMCAS microparticles.**

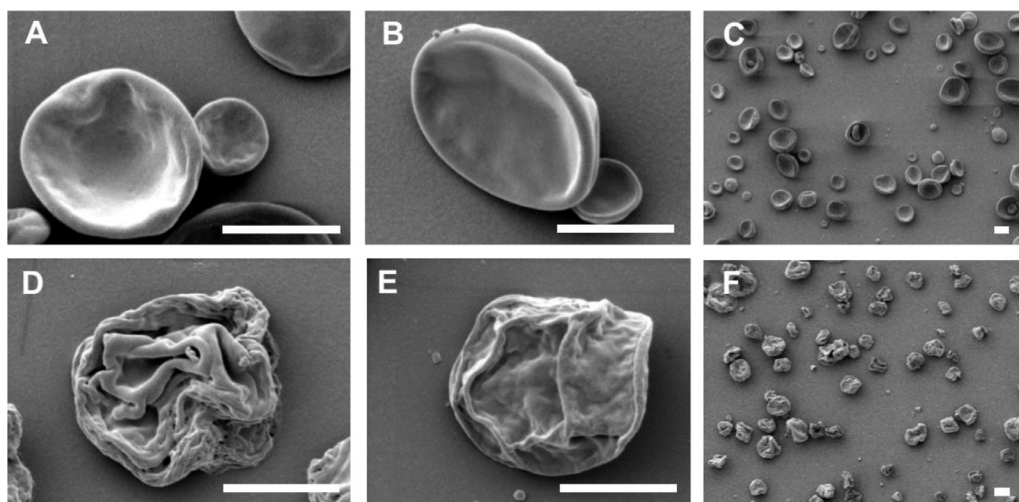


Fig. 3 – Representative SEM images of microparticles prepared with ACE (A, C), ACE-EtOH (B), ACE-H₂O (D) and EtOH-H₂O (E, F). The scale bars indicate 2 μm.

pared with the poorer solvent mixtures [36,37]. Polymer chains are more extended in good solvents resulting in a higher viscosity and previous studies have demonstrated that larger microparticles are formed due to the higher viscosity and larger droplets as well as the lower mobility of the polymer in the evaporating droplet [38,39]. Yet, the differences observed in particle size were modest.

Nevertheless, the differences in the morphology of microparticles prepared with different solvent mixtures were more pronounced (Fig. 3). None of the microparticles prepared were spherical but were instead more disk shaped and flat, indicating that the forming microparticles had collapsed during solvent evaporation. The phenomenon is explained by the slow diffusion of high molecular weight polymer, which cannot follow the evaporation of solvent, thus forming a hollow structure that later collapses [40]. This is also often observed for drying of colloidal suspensions and is known as the “coffee ring effect” [41]. Microparticles prepared with ACE and ACE-EtOH showed smooth surfaces, while microparticles prepared with ACE-H₂O and EtOH-H₂O were corrugated with a rough surface. The degree of roughness of surface was correlated with the solubility of HPMCAS in the solvent used and similar observations on surface morphology has been observed in previous studies [25,31]. It was also observed that the obtained microparticles were not agglomerated during storage, assuming that the residual solvent did not affect the physical stability of the microparticles.

3.4. Surface chemistry analysis

The percentage of CEL on the particle surface was detected by atomic concentration of F, N and S atoms, which are not present in the HPMCAS, and is shown in Table 3. The drug loading efficiency indicated that the total amount of drug in the microparticles was close to the original concentration added to the feed solution before electrospraying. Surface chemistry analysis showed that the surface of CEL-loaded microparticles have a CEL concentration between 19% and 25%,

Table 3 – Surface chemical composition of CEL-loaded HPMCAS microparticles prepared from the different solvent systems.

Solvent	N/F	S/F	F/C	CEL concentration (%)
ACE	0.885	0.308	0.044	22.7 ± 0.3
ACE-EtOH (85:15)	0.862	0.310	0.050	25.4 ± 1.9
ACE-H ₂ O (85:15)	0.828	0.310	0.060	25.3 ± 2.1
EtOH-H ₂ O (85:15)	1.000	0.364	0.051	19.3 ± 1.5

indicating a relatively homogenous distribution of CEL within the microparticles. Microparticles prepared with EtOH-H₂O had the lowest surface CEL concentration. This could be explained by an early precipitation of CEL as the EtOH evaporates and the H₂O concentration increases in the evaporating droplet. Later precipitation of CEL may allow the CEL molecules to diffuse out to the particle surface through the polymer network. However, differences in surface CEL concentration were relatively minor. The results are partially in agreement with the observations from particle size and morphology where the solubility of HPMCAS in the solvent mixture influenced the particle formation, although with the additional influence of CEL solubility. The process is complex due to the balance between polymer precipitation, drug diffusion in the polymer matrix, and the evaporation of the two solvents in the mixtures.

3.5. Drug release study

Drug release studies demonstrated a substantial improvement in the dissolution rate of electrosprayed solid dispersions compared with the crystalline CEL powder and the physical mixture of CEL and HPMCAS (Fig. 4). Crystalline CEL and physical mixture of CEL and HPMCAS both resulted in approx. 5% drug release after 4 h, indicating no influence of physically blended HPMCAS on CEL dissolution at this small amount. At

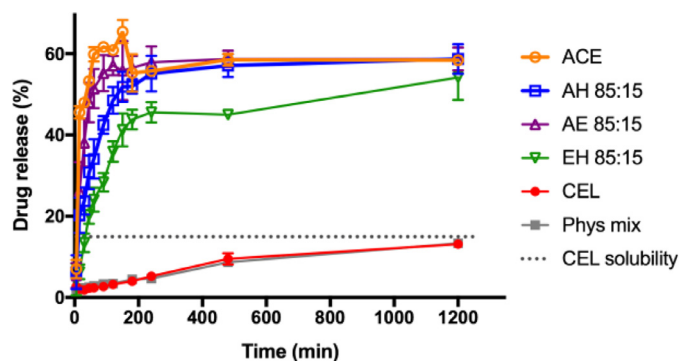


Fig. 4 – Drug release from electrospayed microparticles in PBS. Values are presented as the mean \pm SD ($n = 3$).

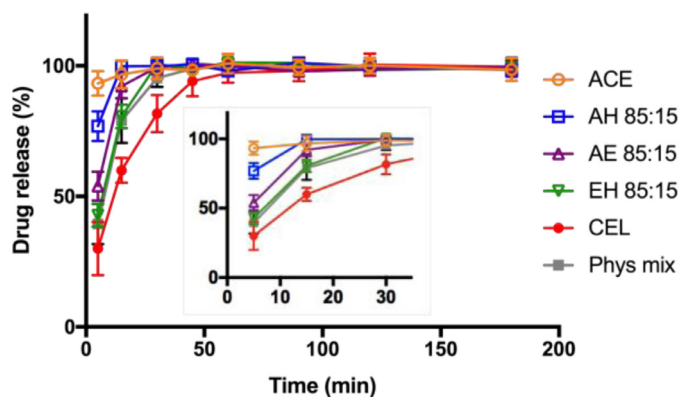


Fig. 5 – Drug release from electrospayed microparticles in PBS with 1.5% SLS. Values are presented as the mean \pm SD ($n = 3$).

the same time the electrospayed solid dispersions demonstrated 45%–65% drug release indicating a 10-fold increase in dissolution rate. For all electrospayed samples CEL was supersaturated and remained supersaturated at approximately 4 times the equilibrium solubility of CEL for the duration of the dissolution study.

This indicates that HPMCAS facilitated the dissolution of CEL and subsequently prevented the recrystallization of CEL in the dissolution medium by interacting with the dissolved CEL molecules, as observed in other studies [42,43]. The results demonstrate that the parachute effect of HPMCAS occurred at a relatively low concentration of 22 $\mu\text{g/ml}$.

All electrospayed samples reached a drug release of 55%–60% with slight differences in the dissolution rate between the samples. Solid dispersions prepared with ACE released the quickest followed by those prepared in ACE–EtOH, ACE–H₂O and EtOH–H₂O, respectively. This is directly contradictory to the size and morphology findings where microparticles prepared with ACE and ACE–EtOH were larger with a smooth surface and were therefore expected to result in slower dissolution than the smaller microparticles with rough surfaces prepared using ACE–H₂O and EtOH–H₂O. This could possibly be explained by differences in the drug distribution where microparticles prepared with ACE, ACE–EtOH and ACE–H₂O exhibited a higher surface drug loading compared with those prepared with EtOH–H₂O. Although in this study drug release was only tested in release media with a pH above 6.8, it is expected that microparticle disintegration and drug release

would not take place at low pH values below 5.5 due to the pH dependent solubility of HPMCAS.

The drug release from electrospayed solid dispersions was also studied under sink conditions with addition of SLS (CEL solubility > 1 mg/ml) (Fig. 5). Here a full dissolution of the added CEL is observed as expected and only small variations in the dissolution rate are detected for the different electrospayed samples. As under non-sink conditions the electrospayed samples showed a faster drug release compared with crystalline CEL and the physical mixture of CEL and HPMCAS. In this case, the physical mixture showed a slightly faster dissolution rate compared with CEL. The drug release from electrospayed samples was again slightly dependent on the solvent mixture used for preparation and again the same trend was observed. Microparticles prepared with ACE had the fastest release while microparticles prepared with EtOH–H₂O had the slowest drug release. This suggests that the microparticles prepared using different solvent mixtures have differences in drug distribution as well as polymer conformation, which results in differences in their drug release kinetics. Those with the fastest drug release (ACE, AH 85:15) also showed higher solubility for both polymer and drug and are likely to have a finer drug dispersion in the polymer matrix, resulting in quicker drug dissolution rate. These findings show that solvent mixtures can be used as a way to vary the solubility of the solutes in the feed solution and thereby modifying the characteristics and the drug release from the resulting microparticles.

4. Conclusion

HPMCAS solid dispersions loaded with CEL were prepared by electrospraying using different feasible solvent mixtures to investigate if the particle characteristics and drug release profiles were influenced by the solvent composition. All CEL-loaded HPMCAS microparticles produced by electrospraying were amorphous and their size and morphology were dependent on the solubility of HPMCAS in the solvent mixture. All microparticles resulted in rapid release of CEL and maintained a supersaturation 4 times higher than the solubility of CEL based on the precipitation inhibition by HPMCAS. Owing to the different solubility of CEL and HPMCAS in solvent mixtures, the electrospraying solvent mixtures influenced the morphology, the surface drug distribution and the release profiles of microparticles. The present study highlighted the feasibility to enhance the release of poorly water-soluble drug and inhibit the recrystallization by using electrosprayed HPMCAS solid dispersion, and the possibility to alter the particle characteristics by modifying solvent composition.

Conflicts of interest

The authors report no conflicts of interest associated with this manuscript. The authors alone are responsible for the content and writing of this manuscript.

Submission declaration

All authors have contributed to the conception and design of the study and acquisition, analysis and interpretation of data. All authors have drafted the article and revised it critically for important intellectual content. All authors have approved the final article. The authors certify that this manuscript, or any part of it, has not been published and will not be submitted elsewhere for publication while being considered by the Asian Journal of Pharmaceutical Sciences.

Role of funding source

The Danish research council provided financial support for the conduct of the research. The funding source had no involvement in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

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REFERENCES

- [1] Hauss DJ. Oral lipid-based formulations. *Adv Drug Deliv Rev* 2007;59(7):667–76.
- [2] Loebmann K, Grohgan H, Laitinen R, Strachan C, Rades T. Amino acids as co-amorphous stabilizers for poorly water soluble drugs – Part 1: preparation, stability and dissolution enhancement. *Eur J Pharm Biopharm* 2013;85:873–81.
- [3] Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. *ISRN Pharm* 2012.
- [4] Junyaprasert VB, Morakul B. Nanocrystals for enhancement of oral bioavailability of poorly water-soluble drugs. *Asian J Pharm Sci* 2015;10(1):13–23.
- [5] Sekiguchi K, Obi N. Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. *Chem Pharm Bull* 1961;9(11):866–72.
- [6] Serajuddin ATM. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. *J Pharm Sci* 1999;88(10):1058–66.
- [7] Streubel A, Siepmann J, Bodmeier R. Drug delivery to the upper small intestine window using gastroretentive technologies. *Curr Opin Pharmacol* 2006;6(5):501–8.
- [8] Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. *Drug Discov Today* 2007;12(23):1068–75.
- [9] Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications. *Int J Pharm* 2011;420(1):1–10.
- [10] Berkland C, King M, Cox A, Kim K, Pack DW. Precise control of PLG microsphere size provides enhanced control of drug release rate. *J Control Release* 2002;82(1):137–47.
- [11] Klose D, Siepmann F, Elkharrak Z, Krenzlin S, Siepmann J. How porosity and size affect the drug release mechanisms from PLGA-based microparticles. *Int J Pharm* 2006;314(2):198–206.
- [12] Xua S, Dai WG. Drug precipitation inhibitors in supersaturable formulations. *Int J Pharm* 2013;453(1):36–43.
- [13] Curatolo W, Nightingale JA, Herbig SM. Utility of hydroxypropylmethylcellulose acetate succinate (HPMCAS) for initiation and maintenance of drug supersaturation in the GI milieu. *Pharm Res* 2009;26(6):1419–31.
- [14] Friesen DT, Shanker R, Crew M, Smithey DT, Curatolo WJ, Nightingale JAS. Hydroxypropyl methylcellulose acetate succinate-based spray-dried dispersions: An overview. *Mol Pharm* 2008;5(6):1003–19.
- [15] Chiou WL. Pharmaceutical applications of solid dispersion systems: X-ray diffraction and aqueous solubility studies on griseofulvin-polyethylene glycol 6000 systems. *J Pharm Sci* 1977;66(7):989–91.
- [16] Won DH, Kim MS, Lee S, Park JS, Hwang SJ. Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical anti-solvent precipitation process. *Int J Pharm* 2005;301(1–2):199–208.
- [17] Paudel A, Worku ZA, Meeus J, Guns S, Van Den Mooter G. Manufacturing of solid dispersions of poorly water soluble drugs by spray drying: formulation and process considerations. *Int J Pharm* 2013;453(1):253–84.
- [18] Bohr A, Kristensen J, Stride E, Dyas M, Edirisinghe M. Preparation of microspheres containing low solubility drug compound by electrohydrodynamic spraying. *Int J Pharm* 2011;412(1–2):59–67.
- [19] Jaworek A, Sobczyk AT. Electrospraying route to nanotechnology: an overview. *J Electrostat* 2008;66(3–4):197–219.
- [20] Gao Y, Chang M-W, Ahmad Z, Li J-S. Magnetic-responsive microparticles with customized porosity for drug delivery. *RSC Adv* 2016;6(91):88157–67.
- [21] Gao Y, Bai Y, Zhao D, Chang M-W, Ahmad Z, Li J-S. Tuning microparticle porosity during single needle electrospraying synthesis via a non-solvent-based physicochemical approach. *Polymers* 2015;7(12):2701–10.

- [22] Bohr A, Kristensen J, Dyas M, Edirisinghe M, Stride E. Release profile and characteristics of electrosprayed particles for oral delivery of a practically insoluble drug. *J R Soc Interface* 2012;9(75):2437–49.
- [23] Bohr A, Boetker JP, Rades T, Rantanen J, Yang M. Application of spray-drying and electrospraying/electrospinning for poorly water-soluble drugs: a particle engineering approach. *Curr Pharm Des* 2014;20(3):325–48.
- [24] Bock N, Woodruff MA, Huttmacher DW, Dargaville TR. Electrospraying, a reproducible method for production of polymeric microspheres for biomedical applications. *Polymers* 2011;3(1):131–49.
- [25] Almería B, Deng W, Fahmy TM, Gomez A. Controlling the morphology of electrospray-generated PLGA microparticles for drug delivery. *J Colloid Interface Sci* 2010;343(1):125–33.
- [26] Bohr A, Wan F, Kristensen J, Dyas M, Stride E, Baldursdóttir S, et al. Pharmaceutical microparticle engineering with electrospraying: the role of mixed solvent systems in particle formation and characteristics. *J Mater Sci Mater Med* 2015;26(2):61.
- [27] Chawla G, Gupta P, Thilagavathi R, Chakraborti AK, Bansal AK. Characterization of solid-state forms of celecoxib. *Eur J Pharm Sci* 2003;20(3):305–17.
- [28] Klar F, Urbanetz NA. Solubility parameters of hypromellose acetate succinate and plasticization in dry coating procedures. *Drug Dev Ind Pharm* 2016;42(10):1621–35.
- [29] Hansen, Charles M. Hansen solubility parameters: a user's handbook. CRC press 2013: 1689–1699
- [30] European Pharmacopoeia Commission. European directorate for the quality of medicines & healthcare. European Pharmacopoeia. Council of Europe; 2014. p. 2963.
- [31] Bohr A, Yang M, Baldursdóttir S, et al. Particle formation and characteristics of Celecoxib-loaded poly(lactic-co-glycolic acid) microparticles prepared in different solvents using electrospraying. *Polymer* 2012;53(15):3220–9.
- [32] Enayati M, Ahmad Z, Stride E, Edirisinghe M. One-step electrohydrodynamic production of drug-loaded micro- and nanoparticles. *J R Soc Interface* 2010;7(45):667–75.
- [33] Peltonen L, Valo H, Kolakovic R, Laaksonen T, Hirvonen J. Electrospraying, spray drying and related techniques for production and formulation of drug nanoparticles. *Expert Opin Drug Deliv* 2010;7(6):705–19.
- [34] Kawakami K, Zhang S, Chauhan RS, et al. Preparation of fenofibrate solid dispersion using electrospray deposition and improvement in oral absorption by instantaneous post-heating of the formulation. *Int J Pharm* 2013;450(1–2):123–8.
- [35] Mehta P, Haj-Ahmad R, Rasekh M, et al. Pharmaceutical and biomaterial engineering via electrohydrodynamic atomization technologies. *Drug Discov Today* 2017;22(1):157–65.
- [36] Wan F, Wu JX, Bohr A, et al. Impact of PLGA molecular behavior in the feed solution on the drug release kinetics of spray dried microparticles. *Polymer* 2013;54(21):5920–7.
- [37] Tanno F, Nishiyama Y, Kokubo H, Obara S. Evaluation of hypromellose acetate succinate (HPMCAS) as a carrier in solid dispersions. *Drug Dev Ind Pharm* 2004;30(1):9–17.
- [38] Yang JT. The viscosity of macromolecules in relation to molecular conformation. *Adv Protein Chem* 1962;16:323–400.
- [39] Debye P, Bueche AM. Intrinsic viscosity, diffusion, and sedimentation rate of polymers in solution. *J Chem Phys* 1948;16(6):573–9.
- [40] Hong Y, Li Y, Yin Y, Li D, Zou G. Electrohydrodynamic atomization of quasi-monodisperse drug-loaded spherical/wrinkled microparticles. *J Aerosol Sci* 2008;39(6):525–36.
- [41] Nikolov AD, Wasan DT. Mechanisms of the assembly of nano- and microparticle two-dimensional structures in a wedge film. *Ind Eng Chem Res* 2008;48(5):2320–6.
- [42] Brouwers J, Brewster ME, Augustijns P. Supersaturating drug delivery systems: The answer to solubility-limited oral bioavailability? *J Pharm Sci* 2009;98(8):2549–72.
- [43] Guzmán HR, Tawa M, Zhang Z, et al. Combined use of crystalline salt forms and precipitation inhibitors to improve oral absorption of celecoxib from solid oral formulations. *J Pharm Sci* 2007;96(10):2686–702.